CLAIMS

What is claimed is:

1. A method of predicting the susceptibility of a reactive site on a molecule to metabolism, the method comprising:
a) receiving a value of an electronic contribution to reactivity for the site;
b) calculating an accessibility correction factor for the site;
c) applying the accessibility correction factor to the initial activation energy value to generate a new reactivity value for the site; and
d) outputting the new reactivity value for the site.

2. The method of claim 1 wherein (a), (b), (c), and (d) are repeated for multiple reactive sites on the substrate molecule.

3. The method of claim 2, further comprising determining which of the multiple reactive sites is most likely to undergo metabolism.

4. The method of claim 1 wherein the molecule accessibility correction factor is calculated for a cytochrome P450 enzyme.

5. The method of claim 1, wherein the accessibility correction factor reflects how the molecule can orient itself in a metabolic enzyme.

6. The method of claim 1, wherein the accessibility correction factor reflects steric constraints on the accessibility of the site.

7. The method of claim 1, wherein applying the accessibility correction factor to the initial activation energy value comprises summing the accessibility correction factor and the initial activation energy.

8. The method of claim 1, wherein the accessibility correction factor is a function of one or more accessibility descriptors.

9. The method of claim 1, wherein the one or more accessibility descriptors are selected from the group consisting of orientation accessibility descriptors and combinations thereof.

10. The method of claim 1, wherein the one or more accessibility descriptors are selected from the group consisting of steric accessibility descriptors and combinations thereof.

11. The method of claim 1, wherein applying the accessibility correction factor to the initial activation energy value comprises employing the following expression:

$$E_{A\,corr} = E_{A,0} + \sum_{i}^{N\,steric\,descriptors} C_i K_i + \sum_{j}^{M\,orientation\,descriptors} C_j K_j$$

wherein E_{Acorr} is the new reactivity value for the site, wherein E_{A0} is the electronic contribution to reactivity for the site, wherein the C_is and C_js are coefficients for steric and orientation descriptors, respectively, and wherein the K_is and K_js are steric and orientation descriptors.

12. The method of claim 1, wherein the accessibility correction factor reflects an amphoteric effect manifest the molecule.

13. The method of claim 12, wherein the amphoteric effect is calculated by
a) calculating a surface area of each atom on the molecule;
b) calculating a partial charge of each atom on the molecule;
c) calculating an amphoteric moment;
d) extending a vector from a reference point to the reactive site on the molecule;
e) outputting an amphoteric correction factor.

14. The method of claim 1, wherein the accessibility correction factor corrects for a surface area accessibility at the reactive site on the molecule.

15. The method of claim 1, wherein calculating the surface area accessibility correction factor comprises:
a) choosing a probe radius;
b) determining the exposed surface area of an atom in the reactive site;
c) comparing the exposed surface area to a reference value; and
d) outputting a surface area correction factor.

16. The method of claim 15wherein the probe radius is the radius of a solvent molecule.

17. The method of claim 15 wherein the reference value is the surface area of a hydrogen in a methyl group on an aliphatic chain.

18. The method of claim 15 wherein the reference value is the surface area of a carbon in an aromatic group.

19. The method of claim 1, wherein the accessibility correction factor reflects a parabolic curvature effect at the reactive site on the molecule.

20. The method of claim 19, wherein calculating the parabolic curvature accessibility correction factor comprises:
a) identifying a point on or near one of the atoms in the reactive site;
b) parameterizing at least one parabola using a point on or near an atom that is within about 10A of the atom in the reactive site; and
c) outputting a parabolic curvature correction factor.

21. The method of claim 1, wherein the accessibility correction factor reflects protrusion accessibility effects at the reactive site on the molecule.

22. The method of claim 21, wherein calculating the protrusion accessibility correction factor comprises:

a) choosing an atom in the reactive site;
b) extending a vector from a standard point in the molecule to the atom;
c) assigning a score to the vector; and
d) outputting an protrusion accessibility correction factor.

23. The method of claim 1, wherein the accessibility correction factor reflects extension accessibility effects at the reactive site on the molecule.

24. The method of claim 23, wherein calculating the extension accessibility correction factor comprises:
a) choosing an atom in the reactive site;
b) extending a vector from a standard point in the molecule to the atom;
c) assigning a score to the vector; and
d) outputting an extension accessibility correction factor.

25. The method of claim 1, wherein the accessibility correction factor reflects distance to polar regions effects at the reactive site of the molecule.

26. The method of claim 25, wherein calculating the distance to polar regions effects accessibility correction factor comprises:
a) calculating the polarity of each atom on the molecule;
b) identifying at least one range of distances from the reactive site;
c) determining the amount of polarity within each range;
d) outputting a distance to polar regions correction factor for each range.

27. The method of claim 25, wherein the distance to polar regions effects correction factor is weighted by the protrusion of atoms in the range.

26. The method of claim 1, wherein the accessibility correction factor reflects hydrophobicity effects at the reactive site of the molecule.

27. The method of claim 26, wherein calculating the hydrophobicity effects accessibility correction factor comprises:
a) identifying a reactive atom in the reactive site;
b) identifying atoms connected to the reactive atom;
c) calculating the surface area of at least some of the connected atoms;
d) calculating the partial charge of at least some of the connected atoms;
e) outputting a hydrophobicity effects correction factor.

28. The method of claim 1, wherein the accessibility correction factor reflects the distance to charged atoms effects at the reactive site of the molecule.

29. The method of claim 28, wherein calculating the distance to charged atom effects accessibility correction factor comprises:
a) identifying a reactive atom in the reactive site;
b) calculating the partial charge of atoms on the molecule;
c) identifying a threshold charge;
d) calculating the distance from the reactive atom on the molecule;

e) identifying a threshold distance or threshold degree of connectivity to the reactive atom;
f) outputting a distance to charged atoms effects accessibility correction factor.